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Leukemic Thyroiditis as the Initial Relapsing Sign in a Patient With Acute Lymphocytic Leukemia and Blast Expression of the Neural Cell Adhesion Molecule

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We report a patient with a history of T-cell ALL in remission who presented with symptoms and laboratory values consistent with subacute thyroiditis but was found to have leukemic thyroiditis as the first clinical manifestation of leukemic relapse. Bone marrow examination at this time demonstrated recurrent ALL. After successful re-induction with chemotherapy and an allogeneic bone marrow transplant this patient developed an isolated recurrence of her ALL manifested by symptomatic thyromegaly and a new mediastinal mass that was treated with irradiation. Despite no medullary recurrence of ALL, the patient developed pleuritic chest pain and shortness of breath and succumbed to pericardial extramedullary leukemia 9 months later. This to our knowledge is the third reported case of symptomatic ALL involvement of the thyroid gland and the first to be confirmed histologically. Furthermore, this patient had blast expression of the neural cell adhesion molecule (CD56), a cell surface marker that has not been studied in ALL but has previously been identified as a risk factor for extramedullary leukemia (EML) in acute non-lymphocytic leukemia. The authors hypothesize that CD56 expression in this patient might have contributed to her predisposition to EML. Am. J. Hematol. 55:212–215, 1997. © 1997 Wiley-Liss, Inc.†

Key words: acute lymphocytic leukemia, thyroiditis, extramedullary leukemia, neural cell adhesion molecule

INTRODUCTION

Extramedullary leukemia is a common manifestation of acute lymphocytic leukemia (ALL) that can occur at presentation, as an isolated extramedullary recurrence, and at the time of medullary relapse. Sites of extramedullary involvement at presentation of ALL most often include the meninges, lymph nodes, spleen, and liver. Similarly, meningeal and testicular relapses are the most common form of extramedullary relapses seen in ALL and therefore have relatively defined treatment plans [1–3]. Other sites of involvement such as the eye, kidney, skin, bone, pleura, pericardium, spine, and colon have also been less commonly noted in ALL patients [3–7]. Involvement of the thyroid gland at any time during the course of ALL is extremely rare with only two previously reported cases [8,9]. This low propensity for ALL to involve the thyroid is further demonstrated by only a 5% incidence of thyroid involvement in autopsied patients who died as a direct consequence of ALL with a 83% incidence of EML elsewhere [10].

Factors that have been previously identified as risk factors for the development of EML in modern treated patients with ALL include a high presenting white blood cell count, T-cell subtype, and a previous history of EML. While the neural cell adhesion molecule (NCAM,

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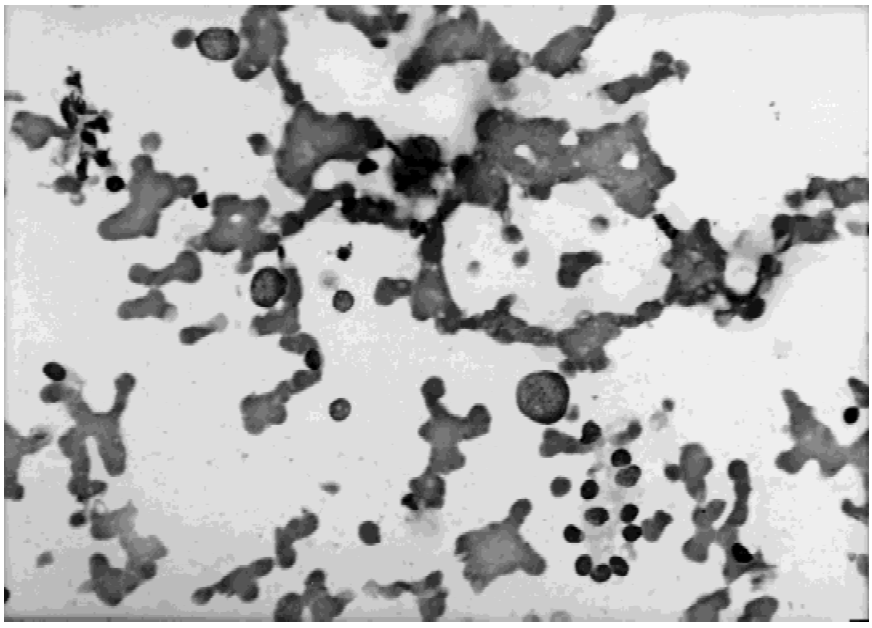

Fig. 1. Fine needle aspirate of the thyroid gland demonstrating large leukemic blasts (arrow) interspersed among smaller follicular thyroid cells.

CD56, Leu-19) has been associated with EML in patients with acute myeloid leukemia and peripheral T-cell lymphoma, its possible similar role in ALL has not been defined.

We report a patient with a history of T-cell ALL in remission who presented with painful leukemic infiltration of the thyroid as the first clinical sign of relapse who was subsequently found to have blast expression of NCAM. The possible role of NCAM expression in predisposing to our patient's EML is discussed.

CASE REPORT

The patient was a 21-year-old female who presented in November 1991 with substernal chest pain, dyspnea, recent onset headache, and facial swelling. Physical examination demonstrated a 2 cm mass in the isthmus of thyroid, facial edema, and bilateral axillary lymphadenopathy. A chest X-ray was notable for an anterior mediastinal mass. The peripheral leukocyte count was 26.9×10^9 with 36% of the cells being blasts. A bone marrow biopsy revealed greater than 90% blasts with strong acid phosphatase staining and a morphology consistent with T-cell ALL FAB-L2. Flow cytometry demonstrated a population of cells co-expressing CD5, CD7 with variable co-expression of CD10 and CD34 (CD56 and CD15 not done). The pathology was confirmed at an outside institution as part of central review for Cancer and Leukemia group B (CALGB) study 9111. Cytogenetics demonstrated a 92, XXYY karyotype. Treatment on CALGB 9111 utilizing cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase induction resulted in both complete resolution of the anterior mediastinal mass and the medullary leukemia. Treatment with early intensification, central nervous system prophylaxis, and late intensification followed. In September 1992 maintenance therapy was begun with all bone marrow biopsies during this time having less than 5% blasts. In May 1993 she noted neck swelling and had slight thyromegaly prompting an endocrine evaluation which demonstrated a 30 g diffusely enlarged and tender thyroid with normal thyroid function tests and negative thyroglobulin and microsomal antibodies leading to the presumptive diagnosis of subacute thyroiditis. The patient noted progressive thyromegaly and shortness of breath leading to a thyroid biopsy that revealed leukemic thyroiditis (Fig. 1). A bone marrow biopsy at this time revealed 68% blast cells with the flow cytometry phenotype demonstrating predominately CD5, CD15, CD38, CD34, CD33, and CD56 expression. Equivocal expression of CD7 was also noted.

The patient underwent successful re-induction therapy followed by an allogeneic bone marrow transplant. Symptoms of neck swelling and shortness of breath developed in May 1994 leading to a CT scan which demonstrated a large anterior mediastinal mass extending from the previous site of thyroid involvement to the aortic arch. Treatment with corticosteroids and radiation therapy was initiated and a biopsy soon after was nondiagnostic for leukemic recurrence. Bone marrow biopsy at this time revealed no evidence of leukemia. The patient was observed without further therapy until Novem-

ber 1994 when she noted recurrent chest pain and shortness of breath. Extensive evaluation at this time was unrevealing. The chest pain persisted and the patient was diagnosed with pericardial and mediastinal leukemic involvement prior to her death from ALL in February 1995.

DISCUSSION

To our knowledge, this case represents the third reported case of symptomatic leukemic infiltration of the thyroid in a patient with ALL. Unlike the two previously reported cases, in which no biopsy was performed premortem, our patient had histologically confirmed leukemic thyroiditis. The clinical symptoms of thyroid enlargement and tenderness are also unique to the two previous cases where either asymptomatic thyroid enlargement or symptoms of hypothyroidism predominated. While our patient's symptoms were initially suggestive of a subacute thyroiditis, progressive symptoms led to a thyroid aspirate that exhibited a dual population of large single blast cells interspersed with small follicular cell fragments. The blasts exhibited a high nuclear to cytoplasmic ratio with some having very little visible cytoplasm. Their nuclear size and shape varied with some exhibiting irregular nuclear contours. The nuclei exhibited finely granular chromatin and one to several nucleoli. The epithelium present was composed of columnar cells in a ''honeycomb'' pattern with a moderate amount of granular cytoplasm, centrally placed round nuclei with finely granular, evenly distributed chromatin, and inconspicuous nucleoli consistent with benign follicular thyroid tissue. The possibility of peripheral blood contamination was considered but later excluded as a consequence of close proximity of the blast cells and follicular cells throughout the biopsy, the large number of blast cells in the thyroid compared to the peripheral blood, and the rarity of other white blood cells present on the smear that demonstrated the first sign of ALL relapse. Furthermore, these identical symptoms recurred again soon after completion of an allogeneic bone marrow transplant and were again believed to be secondary to recurrent leukemic thyroiditis as demonstrated by a marked response to corticosteroid and radiation therapy. This case demonstrates the importance of diligent monitoring for extramedullary leukemia symptoms in patients with a previous history of ALL in remission. Furthermore, it adds to previous reported cases in confirming the effectiveness of cytologic examination of masses to confirm the clinical suspicion of EML [6,15].

Factors predisposing to extramedullary manifestations in ALL are less defined when compared to patients with acute myelogenous leukemia. T-cell subtype, high presenting white blood cell count, and previously documented EML are all considered risk factors for this complication in ALL. While NCAM has not been identified as a risk factor for EML in ALL patients, its predisposing role in AML is generally accepted [12–15]. NCAM is derived from chromosome 11 [16] and is expressed on neurons and satellite cells of skeletal muscle where it binds homophilically (CD56+ cell to CD56+ cell) to promote neuron and neuromuscular embryogenesis [17,18]. While NCAM is present in normal hematopoetic cells, ovarian, thyroid, testicular, adrenal, and gastrointestinal tissue as well as solid, neural, and plasma cell malignancies, its role is uncertain [19,20]. The presence of NCAM in both peripheral T-cell lymphomas and AML has been associated with unusual extranodal or extramedullary sites of involvement that correspond to anatomic areas known to express NCAM [12–15,21–25]. This is particularly true of AML patients with t(8;21)(q22;q22) who have both a high frequency of spinal granulocytic sarcomas and NCAM expression [12,13,26]. Expression of this homophilic binding adhesion molecule in our patient's blast cells and its known expression in normal thyroid tissue might explain her predisposition to developing recurrent leukemic thyroiditis.

There have been no large immunophenotyping series examining the expression of natural killer cell antigens (CD16 and CD56) in adult or pediatric ALL. Kaplan et al. [27] retrospectively noted that 4 of 14 (29%) patients with T-cell ALL and 0 of 17 individuals with non-T-cell ALL had CD16 expression but these investigators did not examine NCAM expression. Menckenstock et al. [28] described a patient who presented with anemia, lymphadenopathy, hepatosplenomegaly and was found to have T-cell ALL with concomitant sideroblastic anemia prior to his death during induction therapy. Immunophenotypic examination of this patient's bone marrow demonstrated CD2, CD3, CD7, CD16, and T-cell receptor antigen (CD56 not evaluable) while the peripheral blood demonstrated a similar phenotype with expression of CD56.

To our knowledge, our patient represents the second reported patient with ALL with CD56 expression. Her natural history is unusual for ALL both because of the thyroid involvement at first and second relapse and the absence of second medullary relapse despite a local pericardial extramedullary recurrence that directly lead to her demise. While NCAM's predisposing role in this patient's leukemic thyroiditis and predisposition to extramedullary leukemia remains speculative, further investigation into both its expression and relationship to EML in patients with ALL seem warranted.

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